

Message Text

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TO ALL DIPLOMATIC POSTS

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SUBJECT: PHENFORMIN

POSTS REQUESTED TO INFORM HOST GOVERNMENT DRUG CONTROL
AUTHORITIES OF THE FOLLOWING:

HEW SECRETARY SUSPENDS GENERAL MARKETING OF PHENFORMIN. ON
JULY 25, 1977, THE SECRETARY OF HEALTH, EDUCATION, AND WEL-
FARE SUSPENDED THE NEW DRUG APPLICATIONS FOR PHENFORMIN AND
ORDERED AN END TO GENERAL MARKETING WITHIN 90 DAYS (BY
OCTOBER 23, 1977). THIS ACTION WAS TAKEN BECAUSE OF THE
UNACCEPTABLY HIGH RISK OF LACTIC ACIDOSIS ASSOCIATED WITH
THE USE OF THIS DRUG. PHENFORMIN IS AN ORAL HYPOGLYCEMIC
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DRUG CURRENTLY USED IN THE UNITED STATES BY AN ESTIMATED
336,000 PATIENTS. IT IS MARKETING BY CIBA-GEIGY AS DBI AND
DBI-TD AND AS MELTROL BY USV PHARMACEUTICALS.

THE SECRETARY'S ORDER DOES NOT WITHDRAW PHENFORMIN FROM USE
IMMEDIATELY. A 90-DAY TRANSITION PERIOD IS PROVIDED SO THAT
ALL PATIENTS NOW ON PHENFORMIN CAN BE EVALUATED BY THEIR
PHYSICIANS. BY THE END OF THIS TIME, HOWEVER, PHENFORMIN
SHOULD BE REMOVED FROM THE TREATMENT PROGRAM OF ESSENTIALLY
ALL PATIENTS NOW TAKING THE DRUG (SEE SECTION ENTITLED

GUIDELINES FOR PATIENT MANAGEMENT).

THE SECRETARY'S DECISION IS BASED ON AN EXTENSIVE FDA REVIEW OF THE RISKS OF PHENFORMIN BEFORE ITS ENDOCRINOLOGY AND METABOLISM ADVISORY COMMITTEE IN OCTOBER 1976 AND AT AN OPEN HEARING ON MAY 13, 1977. DATA FROM A VARIETY OF SOURCES SHOW THAT PHENFORMIN-ASSOCIATED LACTIC ACIDOSIS OCCURS AT A MUCH HIGHER INCIDENCE THAN IS GENERALLY APPRECIATED. THE ESTIMATED INCIDENCE IS 0.25 TO 4 CASES PER 1,000 USERS PER YEAR, AND DEATH OCCURS IN APPROXIMATELY 50 PERCENT OF CASES. BECAUSE THERE ARE NOW APPROXIMATELY 336,000 PATIENTS ON PHENFORMIN IN THE UNITED STATES, THIS AMOUNTS TO ROUGHLY 50 TO 700 DEATHS PER YEAR.

AN IMPORTANT ASPECT OF THE RISK OF PHENFORMIN IS THAT LACTIC ACIDOSIS CAN OCCUR EVEN IN PATIENTS TAKING THE DRUG AT DOSES OF 100 MG OR LESS WHO HAVE NONE OF THE UNDERLYING RISK FACTORS WHICH PREDISPOSE TO LACTIC ACIDOSIS (E.G., AZOTEMIA OR CARDIOVASCULAR DISEASE). WHILE A NUMBER OF DRUGS CAN CAUSE DEATH IF ADMINISTERED IN EXCESS DOSAGE OR IN THE PRESENCE OF CONTRAINDICATIONS (E.G., GENERAL ANESTHETICS, DIGITALIS, SEDATIVE-HYPNOTICS, INTRAVENOUS FLUIDS, INSULIN), VERY FEW DRUGS APPROVED FOR MARKETING IN UNCLASSIFIED

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THE UNITED STATES CARRY THE RISK OF DEATH WHEN USED APPROPRIATELY UNDER THE APPROVED CONDITIONS OF LABELING.

THE COMPARATIVE RISKS ASSOCIATED WITH SOME OF THESE OTHER DRUGS KNOWN TO CAUSE FATAL ADVERSE REACTIONS WERE TAKEN INTO ACCOUNT IN REACHING THE PHENFORMIN DECISION. AS EXAMPLES, DEATH DUE TO ANAPHYLAXIS FROM PENICILLIN OCCURS IN AN ESTIMATED 0.02 PATIENTS PER 1,000 TREATED. DEATH FROM THROMBOEMBOLISM DUE TO ORAL CONTRACEPTIVES OCCURS IN APPROXIMATELY 0.01 TO 0.03 PATIENTS PER 1,000 TREATMENT YEARS. CASES OF APLASTIC ANEMIA DUE TO CHLORAMPHENICOL, MANY OF WHICH ARE FATAL, OCCUR IN AN ESTIMATED 0.025 CASES PER 1,000 COURSES OF THERAPY. THUS, THE ESTIMATED INCIDENCE OF DEATH DUE TO LACTIC ACIDOSIS IN PATIENTS ON PHENFORMIN IS ON THE ORDER OF 5 TO 80 TIMES HIGHER THAN THAT ASSOCIATED WITH THESE OTHER WIDELY MARKETING DRUGS. THIS IS A DEGREE OF RISK THAT THE SECRETARY AND FDA AND ITS ADVISORS BELIEVE IS NOT COMPATIBLE WITH CONTINUING UNRESTRICTED MARKETING IN VIEW OF THE RELATIVELY LIMITED ROLE OF PHENFORMIN IN THE MANAGEMENT OF MOST DIABETICS AND THE AVAILABILITY OF ALTERNATIVES IN MOST CASES.

THE SECRETARY'S DECISION TO SUSPEND GENERAL MARKETING OF PHENFORMIN WAS ANNOUNCED AT A MEETING ATTENDED BY REPRESENTATIVES OF THE MANUFACTURERS, THE AMERICAN MEDICAL ASSOCIATION, THE AMERICAN DIABETES ASSOCIATION, THE AMERICAN PHARMACEUTICAL ASSOCIATION, THE COMMITTEE ON THE

CARE OF THE DIABETIC, AND THE HEALTH RESEARCH GROUP. FDA IS CONTINUING TO MEET WITH THIS GROUP TO COORDINATE AN ORDERLY PHASE-OUT OF THE DRUG FROM THE GENERAL MARKET-PLACE.

FDA AND HEW RECOGNIZE THAT A DECISION OF THIS TYPE CAUSES PUBLIC CONCERN AND IMPOSES A SPECIAL BURDEN ON DIABETIC PATIENTS AND THEIR PHYSICIANS. WE ARE ATTEMPTING TO MINIMIZE ALARM AND CONFUSION BY SENDING THIS SPECIAL ISSUE
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OF THE DRUG BULLETIN TO ALL HEALTH PROFESSIONALS. ADDITIONAL INFORMATION WILL BE SHARED WITH READERS OF THE BULLETIN WHEN AVAILABLE. IN THE MEANTIME, THE FOLLOWING GUIDANCE IS OFFERED FOR MANAGING PATIENTS DURING THIS 90-DAY TRANSITION PERIOD.

GUIDELINES FOR PATIENT MANAGEMENT: IT IS IMPORTANT FOR PHYSICIANS, PHARMACISTS, AND PATIENTS TO RECOGNIZE THAT THE SECRETARY'S ORDER DOES NOT IMMEDIATELY BAN THE USE OF PHENFORMIN OR REMOVE IT FROM PHARMACIES. A PHASE-OUT PERIOD OF 90 DAYS IS PROVIDED TO PERMIT AN ORDERLY TRANSFER OF PATIENTS TO OTHER THERAPY. THE REGULAR COMMERCIAL CHANNELS OF DISTRIBUTION OF THE DRUG MAY CONTINUE TO OPERATE AT PRESENT. THE DRUG MAY CONTINUE TO BE PRESCRIBED BY PHYSICIANS AND DISPENSED BY PHARMACISTS DURING THIS TRANSITION PERIOD AS NECESSARY FOR THE CARE OF SELECTED PATIENTS.

ALL PATIENTS CURRENTLY TAKING PHENFORMIN SHOULD BE RE-EVALUATED PROMPTLY AND APPROPRIATE ADJUSTMENTS OF THEIR TREATMENT PROGRAMS MADE. EXPERIENCE IN CLINICS THAT HAVE DISCONTINUED THE USE OF PHENFORMIN SUGGESTS THAT PHENFORMIN CAN BE DISCONTINUED WITHOUT APPRECIABLE LOSS OF CONTROL IN SOME PATIENTS; THAT IMPROVED DIETARY MANAGEMENT AND SWITCHING TO, OR INCREASING, THE DOSE OF A SULFONYLUREA WILL BE SUFFICIENT IN OTHERS; AND THAT TRANSFER TO INSULIN WILL BE NECESSARY IN PERHAPS HALF, THOUGH NOT NECESSARILY IMMEDIATELY. ADEQUATE SUPPLIES OF INSULIN ARE AVAILABLE. THERE IS A SMALL GROUP OF MATURITY-ONSET NONKETOTIC DIABETICS IN WHOM USE OF INSULIN POSES SPECIAL HARDSHIPS AND FOR WHOM THE BENEFITS OF PHENFORMIN CLEARLY OUTWEIGH THE RISKS. THIS GROUP MAY BE DEFINED AS PATIENTS:

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1. WHO ARE SYMPTOMATIC; AND
2. WHOSE SYMPTOMS ARE NOT CONTROLLED WITH DIET AND SULFONYLUREAS ALONE OR WHO CANNOT TAKE SULFONYLUREAS BECAUSE

OF NONTOLERANCE OR ALLERGY, AND

3. WHOSE SYMPTOMS ARE CONTROLLED BY THE ADDITION OF PHENFORMIN TO THEIR REGIMEN; AND

4. WHO HAVE NONE OF THE UNDERLYING RISK FACTORS WHICH CONTRAINDICATE THE USE OF PHENFORMIN; AND

5. (A) WHOSE OCCUPATION IS SUCH THAT THE RISK OF HYPOGLYCEMIA FROM INSULIN WOULD THREATEN THEIR JOBS OR BE A HAZARD TO THEM OR OTHERS; OR (B) WHO CANNOT TAKE INSULIN BECAUSE OF SERIOUS MENTAL OR PHYSICAL DISABILITY AND THERE IS NO PRACTICABLE WAY FOR THEM TO RECEIVE ASSISTANCE FROM RELATIVES OR FRIENDS.

EVERY ATTEMPT WILL BE MADE TO DEVISE A WORKABLE MECHANISM TO MAKE PHENFORMIN AVAILABLE TO PATIENTS MEETING THESE CRITERIA. FDA EMPHASIZES, HOWEVER, THAT PATIENTS COVERED BY SUCH A MECHANISM WILL HAVE TO MEET ALL OF THE CRITERIA LISTED. PATIENTS MEETING ONLY SOME OF THESE CRITERIA SHOULD BE SWITCHED TO OTHER TREATMENTS DURING THE 90-DAY TRANSITION PERIOD.

BACKGROUND TO SUSPENSION DECISION: AN ASSOCIATION BETWEEN PHENFORMIN AND LACTIC ACIDOSIS WAS FIRST REPORTED IN THE EARLY 1960'S. SINCE 1964, WARNINGS ABOUT LACTIC ACIDOSIS HAVE BEEN INCLUDED IN THE LABELING OF PHENFORMIN. AS THE ASSOCIATION BETWEEN THE DRUG AND THIS HAZARD BECAME ESTABLISHED AND THE UNDERLYING RISK FACTORS WHICH PREDISPOSE TO LACTIC ACIDOSIS WERE IDENTIFIED, THESE WARNINGS HAVE BEEN EXPANDED AND STRENGTHENED (SEE DRUG BULLETIN, MAY-JULY 1977).

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IN OCTOBER 1976, FDA'S ENDOCRINOLOGY AND METABOLISM ADVISORY COMMITTEE RECOMMENDED THAT PHENFORMIN BE REMOVED FROM THE MARKET ON THE GROUND THAT IN THE VAST MAJORITY OF PATIENTS PHENFORMIN OFFERS NO COMPENSATING BENEFIT SUFFICIENT TO JUSTIFY THE RISK OF LACTIC ACIDOSIS.

THE BUREAU OF DRUGS CONCURRED. AS AN INTERIM MEASURE, HOWEVER, IN JANUARY 1977, THE LABELING OF PHENFORMIN WAS REVISED (A) TO REDUCE THE RECOMMENDED UPPER LIMIT OF DOSAGE FROM 200 TO 100 MG PER DAY AND (B) TO RESTRICT USE OF PHENFORMIN TO SYMPTOMATIC, ADULT-ONSET DIABETICS IN WHOM ADEQUATE CONTROL COULD NOT BE ACHIEVED BY A SULFONYLUREA OR IN WHOM INSULIN COULD NOT BE USED. THE MANUFACTURERS NOTIFIED THE MEDICAL PROFESSION OF THESE CHANGES THROUGH AN ADVERTISING CAMPAIGN.

ON MAY 6, 1977, THE BUREAU OF DRUGS BEGAN FORMAL PROCEEDINGS TO WITHDRAW PHENFORMIN FROM GENERAL MARKETING

BY PUBLISHING IN THE FEDERAL REGISTER A NOTICE OF
OPPORTUNITY FOR A HEARING (NOH) PROPOSING TO WITHDRAW
APPROVAL OF THE NEW DRUG APPLICATIONS. MANUFACTURERS

WERE PERMITTED 60 DAYS TO SUBMIT DATA TO JUSTIFY THE
HOLDING OF AN EVIDENTIARY HEARING BY FDA. THIS IS THE
USUAL ADMINISTRATIVE PROCEDURE FOR WITHDRAWING A DRUG
FROM THE MARKET.

ON APRIL 22, 1977, WHILE FDA WAS PREPARING THE MAY 6
NOTICE, THE HEALTH RESEARCH GROUP, WASHINGTON, D.C., A
CONSUMER ADVOCATE ORGANIZATION, PETITIONED THE SECRETARY
OF HEW TO SUSPEND PHENFORMIN FROM THE MARKET IMMEDIATELY
UNDER THE SPECIAL AUTHORITY OF THE SO-CALLED "IMMINENT
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HAZARD" PROVISIONS OF THE LAW.

ON MAY 13, 1977, THE DIRECTOR OF THE BUREAU OF DRUGS HELD
A PUBLIC HEARING ON THE QUESTION OF WHETHER PHENFORMIN
CONSTITUTED A SUFFICIENT HAZARD TO THE PUBLIC HEALTH THAT
THE USUAL ADMINISTRATIVE PROCEDURES SHOULD BE BY-PASSED
AND MARKETING OF THE DRUG SUSPENDED IMMEDIATELY. THE
BUREAU HEARD EVIDENCE FROM MANUFACTURERS, DIABETES EXPERTS,
REPRESENTATIVES OF THE AMERICAN DIABETES ASSOCIATION AND
THE COMMITTEE FOR THE CARE OF THE DIABETIC, AND OTHER IN-
TERESTED PARTIES. AFTER THE HEARING, FDA SUMMARIZED THE
AVAILABLE EVIDENCE ON THE INCIDENCE OF LACTIC ACIDOSIS AND
OBTAINED ADDITIONAL INFORMATION THROUGH CONSULTATION WITH
HEALTH OFFICIALS IN SWEDEN, FINLAND, NORWAY, AND NEW
ZEALAND. THE OPINIONS OF MANY EXPERTS WERE ALSO CONSIDERED,
AS EXPRESSED IN THE ADVISORY COMMITTEE MEETINGS AND HEARING
HELD BEFORE THE AGENCY.

THIS INFORMATION WAS FORWARDED TO THE SECRETARY OF HEW
ALONG WITH THE RECOMMENDATION OF FDA THAT THE GENERAL
MARKETING OF PHENFORMIN SHOULD BE SUSPENDED BUT ALSO THAT
A MECHANISM SHOULD BE DEVELOPED TO ACCOMMODATE THE NEEDS
OF THE SMALL NUMBER OF PATIENTS FOR WHOM PHENFORMIN PROVIDES
A SPECIAL BENEFIT. THE SECRETARY IS THE ONLY OFFICIAL
AUTHORIZED BY LAW TO SUSPEND THE MARKETING OF A DRUG PRIOR
TO A FULL EVIDENTIARY HEARING. ON JULY 25, 1977, THE
SECRETARY ANNOUNCED HIS DECISION. THE REQUIRED EVIDENTIARY
HEARING ON THE PROPOSAL TO WITHDRAW THE NEW DRUG APPLI-
CATION WILL BE HELD ON A EXPEDITED BASIS.

PHENFORMIN-ASSOCIATED LACTIC ACIDOSIS - A SUMMARY OF
INCIDENCE RATES

THE FOLLOWING TABLE SUMMARIZES THE ESTIMATED INCIDENCE
RATES FOR CASES OF LACTIC ACIDOSIS ASSOCIATED WITH THE USE
OF PHENFORMIN. THE WIDE VARIATION IN ESTIMATED RATES --

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FROM A LOW OF 0.1 TO A HIGH OF 20 PER 1,000 USERS PER YEAR--
 REFLECTS DIFFERING METHODS OF REPORTING AND DIFFERENT DATA
 BASES. THE LOWER VALUES ARE BASED UPON COUNTRYWIDE RE-
 PORTING AND ARE UNDOUBTEDLY UNDERESTIMATES BECAUSE OF UNDER-
 REPORTING. THE HIGHEST ESTIMATES ARE BASED UPON SINGLE
 HOSPITALS AND MAY BE HIGHER THAN THE TRUE INCIDENCE BECAUSE
 OF POSSIBLE REFERRALS OF CASES OF LACTIC ACIDOSIS TO HOS-
 PITALS KNOWN TO HAVE A PARTICULAR INTEREST IN, AND EXPERTISE
 IN, TREATING THIS CONDITION. FDA'S ESTIMATE THAT PHENFORMIN-
 ASSOCIATED LACTIC ACIDOSIS OCCURS IN 0.25 TO 4 CASES PER
 1,000 USERS PER YEAR IS BASED ON DATA IN THE FOLLOWING
 TABLE. THE FDA ESTIMATE IS BASICALLY THE RANGE SHOWN IN
 THIS TABLE EXCEPT THAT THE LOWEST FIGURE (0.1 FOR VOLUNTARY
 REPORTING IN THE UNITED STATES) WAS DISCOUNTED BECAUSE OF
 KNOWN UNDERREPORTING, AND THE TWO HIGHEST FIGURES (12 AND
 20) WERE DISCOUNTED BECAUSE OF TECHNICAL REASONS TO SUSPECT
 THEY ARE SPURIOUSLY HIGH. MORTALITY RATES IN THESE SERIES
 RANGED FROM 25 TO 60 WITH AN OVERALL RATE OF APPROXIMATELY
 50 PCT.

REPORTED LACTIC ACIDOSIS INCIDENCE RATES

REPORTED DATA BASE	INCIDENCE OF WHERE REPORTED	CASES PER
BY	1,000 TREATMENT	
	YEARS	

CIBA-GEIGY U.S., COUNTRY- FDA ENDOCRINOLOGY	0.1
WIDE ADVISORY COMMITTEE,	
1976	

DAVIDOFF U.S., SINGLE PERSONAL COMMUNI-	2 TO 20
HOSPITAL CATION TO FDA	
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IDANPAAN- FINLAND, PERSONAL COMMUNI-	0.2
HEIKKILA COUNTRYWIDE CATION TO FDA	

HOSLE NORWAY, PERSONAL COMMUNI-	0.8#
COUNTRYWIDE CATION TO FDA	

NEW NEW ZEALAND, NEW ZEALAND MED.	4.4
ZEALAND COUNTRYWIDE J. 85:2I, 1977	
MED.J. (BEAVINS)	

PHILLIPS, AUSTRALIA, BRITISH MED.J.	12
P.J., ET SINGLE HOS- 1:234, 1977	
. PITAL	

BENGTSSON, SWEDEN ACTA MEETING 4
K. ET AL. SINGLE SCANDINAVIA
HOSPITAL 191:203, 1972

BERGMAN SWEDEN WHO MEETING 1974 1.6
COUNTRYWIDE APRIL 1977 1975 0.7
1976 0.1

UGDP USA MULTI- DIABETES, VOL. 24, 2.1
CENTER SUPPL. 1, 1975

#ONLY FATAL CASES WERE REPORTED. A MORTALITY RATE OF 50 PCT
WAS ASSUMED TO OBTAIN INCIDENCE OF CASES OF LACTIC ACIDOSIS.
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Secure: OPEN
Status: NATIVE
Subject: PHENFORMIN
TAGS: TBIO, ECEM, XX, US
To: ALL DIPLOMATIC POSTS
Type: TE
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